

Q1 Surgical treatment for hepatocellular carcinoma in cirrhotic patients. Guide to the selection and decision-making process in a context of multimodal strategy

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Received: 6 October 2008 / Accepted: 10 November 2008

Abstract Hepatocellular carcinoma (HCC) is the fifth most frequent malignant tumour and the third leading cause of death due to cancer worldwide [1]. Surgical treatment is the only long-term curative therapy. But the resection rate remains low in cirrhotic patients due to contraindications imposed mainly by hepatic insufficiency and excessively advanced tumoral stages. In recent years, however, due to the extended use of screening programmes in high-risk patients, tumours are smaller at presentation, making treatments easier. In the current context of shortage of organs for transplantation, surgical resection remains the best available treatment option for most patients with HCC in cirrhotic livers. Despite the encouraging results reported by several groups in terms of overall survival, the high recurrence rate is still an unsolved problem. Recently, a large, randomised, placebo-controlled trial has shown that a multikinase inhibitor targeting Ras-kinase and VEGFR-2, sorafenib, improves survival of patients with advanced HCC. Sorafenib was approved by regulatory agencies during 2007 and is likely to become the new standard therapy for HCC patients with advanced disease.

Keywords Hepatocellular carcinoma · Liver carcinoma · Primary liver tumours · Surgery · Surgical · Human

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In what context does HCC appear?

Hepatocellular carcinoma (HCC) usually occurs in patients with liver cirrhosis. The special characteristic of HCC, which make it different to other tumours, is that the prognosis not only depends on tumoral factors but also on the quality of the liver in which it develops. Despite the fact that most patients with HCC have cirrhotic livers, there is a small but well defined percentage of patients without cirrhosis. Our series, with 22% of HCC without liver cirrhosis, is representative of the common experience in the West. This group of patients represents a completely different situation in many aspects; therefore they are not included in this analysis (Fig. 1).

What are the potentially curative treatment options for HCC in cirrhotic patients?

There are three potentially curative modalities competing as a first-line treatment of small, single HCC: hepatic resection, orthotopic liver transplantation (OLT) and percutaneous ablation therapies [2–7]. Each of these treatment approaches has important limitations. Hepatic resection is only applicable to patients with well preserved liver function and normal portal pressure. Percutaneous ablation therapies are especially useful for small (less than 3 cm) tumours, with results clearly inferior to surgical resection in tumours larger than 3 cm. OLT, the ideal treatment for HCC because it not only eliminates the tumour but also the tumorigenic cirrhotic liver, is not a realistic option for many patients due to the shortage of organs for transplantation [2–7].

What is the role of transarterial chemoembolisation (TACE) in the treatment of HCC?

This is not a potentially curative option but it is a suitable procedure able to offer effective hepatic control and prolonged survival [8, 9]. Currently, TACE is considered the standard of care for patients with multinodular HCC (intermediate or stage C) according to the Barcelona Clinic Liver Cancer (BCLC) classification [10] (Fig. 2). TACE is a combination of local drug infusion with selective embolisation of the feeding arteries of the liver tumour. The advantage of delivering chemotherapy by hepatic arterial infusion is the administration of a high dose of the drug to the target. The aim of this therapeutic approach is to reduce the tumour size by ischaemic necrosis and direct drug effects. The rationale behind this procedure is that hepatic tumours obtain their blood supply almost exclusively from the hepatic artery. Different types and calibres of microspheres, as well as collagen and gelatine sponges, are used to produce a temporary arterial hepatic occlusion and polyvinyl alcohol is used to obtain permanent embolisation [11]. Currently, doxorubicin is the most used chemotherapeutic agent in such procedures [12]. The most common complication experienced by almost all patients undergoing chemoembolisation is post-embolisation syndrome, with pain in the right upper quadrant, nausea, vomiting, fever and elevation of liver enzymes [13]. A major analgesic, such as morphine, must be used in the procedure. Adequate supportive treatment with antibiotic and antiemetic prophylaxis, dexamethasone and intravenous hydration is strictly necessary until stabilisation of transaminase serum levels and in order to prevent infections. These adverse events are less pronounced when temporary vascular occlusion agents are used. Less common complications are liver abscess, acute liver failure and infarction [13]. DC beads are new embolic microsphere products that can be loaded with doxorubicin before administration. DC beads are new drug delivery systems used to improve drug targeting of the tumours, maximise drug potency and minimise systemic toxicity.

What is the importance of age in HCC patients?

The mean age in our series was 65 years. This aspect is important because they are at the very limit of the age range in which OLT is an option. This means that, in a population like this, hepatic resection as a treatment strategy will not admit, simply because of age, the possibility of OLT as a rescue therapy in those patients in whom recurrences appear. This situation stresses the importance of a proper and careful selection process. On the other hand, the available evidence suggests that the elderly can be offered hepatic resection for HCC with acceptable results [14].

Which patients with HCC can be treated by hepatic resection?

How to select patients for liver resection in order to avoid an unacceptably high perioperative mortality rate is a rather straightforward process taking into consideration mainly the patient's general condition and liver function factors. There is general agreement that liver resection must be offered only to patients with small (less than 5 cm), single HCC, adequately situated to allow segmentectomy, with excellent liver function (Child-Pugh A (five points), normal bilirubin and without ascites) [4]. In this group of patients, Asian centres further select patient for resection based on the indocyanine green retention rate at 15 min (ICG-15) [15], while European centres use mainly the measurement of the hepatic vein portal gradient (HVPG) [16]. Hepatic resection is contraindicated in patients with HVPG > 10 mmHg (Fig. 2).

When is a liver resection contraindicated in HCC patients

Hepatic resection is contraindicated in cirrhotic patients with HCC if any of the following is present: Child-Pugh B or C status; Child-Pugh A and alterations in the ICG-15; HVPG > 10 mmHg; oesophageal varices; tumour size > 5 cm; tumour number > 1; bilobar resection; macrovascular invasion [4].

How much liver can be safely resected in Child-Pugh A cirrhotic patients with HCC?

According to Makuuchi et al. [15], the extent of the liver resection that can be done safely can be determined by the ICG-15 as follows: ICG-15 < 10%: two thirds of the liver; ICG-15 between 10 and 19%: one third; ICG-15 between 20 and 29%: one segment; ICG-15 between 30 and 39%: limited resection; ICG-15 > 40%: enucleation.

What are the eligibility criteria for liver transplantation (OLT) in cirrhotic patients with HCC?

Age younger than 65 years old; no associated disease contraindicating OLT; solitary tumour smaller than 5 cm or up to 3 tumours smaller than 3 cm (Milan criteria). In patients selected according to the Milan criteria, OLT resulted in a 4-year overall survival rate of 75% and recurrence-free rate of 83% [17, 18].

Must eligibility for liver transplantation be expanded beyond Milan criteria?

The University of California, San Francisco (UCSF) included patients with single tumour <6.5 cm diameter or multiple tumours 2 to 3 nodules <4.5 cm with a total tumour diameter <8 cm [19–24]. However, none of the proposed expanded criteria is supported by a robust statistical sample size and/or prospective validation. Transplant units have to face difficult situations which include (a) more and more patients with HCC, including those with the so-called extended criteria referred for OLT and (b) organ shortage and consequently long waiting periods, which are associated with tumour development [25].

How safe is hepatic resection for HCC in cirrhotic patients?

Our perioperative mortality rate of 3% is situated within the limits defined as acceptable and represents the adequacy of the selection criteria we have been using to indicate this treatment modality. The overall postoperative morbidity of 47% in our series is comparable to the results obtained by other authors [26], ascites being the most frequent complication.

What are the long-term results of hepatic resection for HCC in cirrhotic patients?

In our series, the overall survival rates at 1, 3 and 5 years were 85%, 69% and 59%, respectively. These are excellent results that confirm the important role of hepatic resection in well selected patients with HCC and cirrhosis (Fig. 3).

What is the recurrence rate of HCC in cirrhotic patients treated by hepatic resection?

The recurrence rate in our series, like the worldwide experience [26], is high, with 63% at 5 years (Fig. 4). However, to properly understand these results, this high recurrence rate at 5 years must be put into the context of an equally high overall survival rate at 5 years (69%), which is especially significant if we take into account that this overall survival is obtained in a population of patients in whom the mean age at the study entry was 65 years. In other words, despite the presence of recurrence, a significant percentage of patients survive until an age similar to their life expectancy and many of them died of causes other than that of the HCC. In any case, what is evident is that our current criteria of selection improve survival but not recurrence.

How to predict long-term survival and recurrence after hepatic resection in cirrhotic patients with HCC?

The prediction of long-term survival, and even more so, the prediction of recurrence, is a complex issue and many staging systems have been proposed, each of them having its own virtues and weaknesses. The most important, and so far unsolved, problem is represented by the fact that the best predictor of recurrence, that is microvascular invasion, is usually not a preoperative but a postoperative finding. Wayne et al. [27] identified Child-Pugh classification, fibrosis score and Edmonson-Steiner grade as preoperative predictors of survival. The problem with the utilisation of these preoperative predictive factors is that they need the performance of a liver biopsy and many authors are reluctant to perform this procedure. Bilimoria et al. [28] demonstrated the importance of liver fibrosis as a risk factor of death. In their experience, the presence of minimal or no fibrosis was associated with a 7% risk of death from HCC at 5 years and beyond. The presence of fibrosis identified a group with a 58% risk of death in the same period.

What is the role of postoperative predictor factors of recurrence?

Fuster et al. [5] reported postoperative findings such as vascular invasion and satellite nodules as predictors of recurrence, while survival at 3 years was predicted by type of resection, vascular invasion, size of the tumour, satellites and number of nodules. In our own experience, we found three independent predictors of survival: HVPG>10 mmHg, margin invasion and satellite nodules (the last showing a tendency, but without reaching statistical significance). The Cox regression analysis showed as independent predictors of recurrence: the presence of satellite nodules, microvascular invasion, macrovascular invasion, and absence or rupture of the tumoral capsule. These findings confirm and extend those of several previous investigators. With the exception of HVPG and macrovascular invasion, the other predictor factors were mainly postoperative findings. The best predictor of recurrence, microvascular invasion, is a postoperative finding. The recognition that, in many cases, an accurate prediction of the prognosis cannot be obtained preoperatively but only in the postoperative period, mainly through histopathologic examination, led to the necessity for a rescue therapy for those patients identified as belonging to a high-risk group. This rescue therapy is liver transplantation.

What is the best predictor of recurrence and why

is preoperative prediction so difficult?

Patients must be stratified for high or low risk of recurrence. High risk of recurrence after resection is defined by the presence of vascular invasion, satellite nodules, multinodular or poor differentiation. This distinction is important in order to offer liver transplantation to those with a high risk profile even before the actual appearance of recurrence. Microvascular invasion is the missing factor in the preoperative evaluation, not only for hepatic resection but also for liver transplantation. Many of the preoperatively identified prognostic factors are only rough surrogate markers of the one that really matters: microvascular invasion. Tsai et al. [29] reported an association between tumour size and increasing rates of both microvascular and macrovascular invasion. Other authors [30] found the same association between vascular invasion and the number of tumours. Recently, Esnaola et al. [31] reported that poorly differentiated and undifferentiated tumour grades result in a six-fold increase in the risk of vascular invasion in small HCC. The differentiation of HCC is determined based on nuclear pleomorphism according to a grading system described in 1954 by Edmonson and Steiner in patients with HCC. According to Esnaola et al. [31], the best surrogate markers for vascular invasion are: tumour size greater than 4 cm and high-grade histopathology in the Edmonson-Steiner grading classification.

What is the standard staging classification system for HCC?

Several classification systems are available for HCC [32–34]. The BCLC classification has emerged during recent years as the standard classification that is used for trial design and clinical management of patients with HCC. This classification has been endorsed by an EASL panel of experts and the AASLD guidelines and has been externally validated in European and American patient cohorts. The BCLC classification links stage stratification with a recommended treatment strategy and defines standard of care for each tumour stage [35] (Fig. 2). The importance of stage stratification according to standard classification systems for randomised controlled trials (RCTs) becomes immediately evident if we take into account that the 1- and 2-year survival rates of untreated patients randomly assigned to the control arm in 25 RCTs ranged from 10% to 72% and from 5% to 50%, respectively. These widely discrepant figures likely reflect the inclusion of patients with different stages of the disease [35].

Which treatment for which patient? What is the standard of care to compare new treatments in RCTs?

For comparisons of new treatments it is absolutely necessary to have well defined standards of care for each stage. According to the BCLC staging classification, patients with very early HCC (single <2 cm or carcinoma *in situ*) (stage 0) are optimal candidates for resection. Patients with early HCC (single >2 cm, or up to 3 nodules <3 cm) (stage A) are candidates for radical therapy (resection, liver transplantation, or local ablation via percutaneous ethanol injection (PEI) or radiofrequency ablation (RFA)). Patients with intermediate HCC (multinodular, asymptomatic, without vascular invasion or extrahepatic spread) (stage B) benefit from TACE. Patients with advanced HCC, defined as presence of macroscopic vascular invasion, extrahepatic spread or cancer related symptoms (Eastern Cooperative Oncology Group performance status 1 or 2) (stage C) benefit from sorafenib. Patients with end-stage disease (stage D) will receive symptomatic treatment. Treatment strategy will transition from one stage to another upon treatment failure or contraindications for the procedure [35] (Fig. 2).

Why is liver transplantation the best treatment option for hepatocellular carcinoma in cirrhotic patients?

The principal advantage of transplantation over resection is that it eliminates the field of cancerisation associated with hepatitis and fibrosis. In the past, OLT was performed in patients who were not candidates for liver resection due to too far advanced tumour stages and inadequate liver reserves. This policy led to unacceptably high tumour recurrence rates and poor survival. In recent years, however, the results of OLT as a primary treatment of HCC showed an important and progressive improvement. Yoo et al. [36], analysing the UNOS database, reported improvements over the past 15 years in the 5-year survival rate after liver transplantation in patients with HCC. The figures for the periods of 1987–1991, 1992–1996 and 1997–2001 were 25%, 47% and 61%, respectively. These results are mainly the consequence of a better selection process. However, recurrence, even after transplantation, is high, at roughly 20%. This can be explained because the widely used Milan criteria [17] are based solely on imaging criteria (tumour size, tumour number and macroscopic vascular invasion) without an insight into the biology of the tumour.

Hepatic resection and liver transplantation. Competing options or complementary treatments?

Hepatic resection can be used as a treatment for HCC prior to OLT in three different settings. First, resection can be used as a primary therapy, and OLT reserved as a salvage therapy for patients who develop recurrence or liver failure. Second, resection can be used as an initial therapy to select patients who might obtain benefit from OLT according to

detailed pathological examination of the tumour and the surrounding liver parenchyma. Third, resection can be used as a bridge therapy for patients who have already been enlisted for OLT [25].

What seems to be the most suitable combined strategy of hepatic resection and liver transplantation?

The shortage of organs for transplantation makes the use of OLT as an initial therapy an unrealistic approach for many patients. Based on our experience, with the excellent results in terms of perioperative mortality and long-term overall survival obtained with liver resection in well selected patients, with the only drawback a high recurrence rate, we suggest the selective use of OLT as a rescue procedure in patients with vascular invasion, margin invasion, satellites or absence of capsule.

What are the advantages of hepatic resection followed by salvage transplantation?

It gives rapid access to an effective therapy, without a need for a donor and the corresponding prolonged waiting time. Resection is far less complex than OLT and less demanding in the long term; in selected patients, it offers 5-year survival rates exceeding 50% with good quality of life. In the case of tumour recurrence or deterioration of liver function it remains possible to perform salvage transplantation, without a significant decrease in post-OLT survival compared to patients who primarily underwent OLT. Since transplantation is only performed at the time of recurrence, exposure to immunosuppressive therapy is delayed and the most obvious advantage is that compared with OLT as a primary treatment, it spares organs for transplantation [25].

What are the limitations of the strategy of hepatic resection as a first-line treatment followed by salvage transplantation?

Resection as a first-line treatment for patients with small HCC with preserved liver function, followed by salvage transplantation only for recurrence or liver failure, has been shown to be a feasible strategy as up to 80% of patients with tumour recurrence may still be amenable to transplantation according to the experience of Poon et al. [37]. However, all candidates for salvage OLT in this series from Hong Kong had hepatitis B virus infection (HBV). In Western countries the situation is completely different because the majority of patients have hepatitis C virus (HCV) infection. In this setting, up to 60% of patients at the time of recurrence are over Milan criteria. Possibly due to a dif-

ferent natural history, the majority of HCV-infected patients had multifocal tumours and/or vascular invasion at the time of recurrence, precluding salvage transplantation. Another important difference between HBV- and HCV-infected HCC patients is that HCV-infected patients are, on average, 10 years older at the time of presentation. As was suggested in our experience, this strategy can be limited by two factors associated with age: on the one hand, due to the age limits of eligibility for transplantation, and on the other hand, due to the poor results of liver transplantation in patients older than 65 years [3]. These are the reasons that support the need to identify not only predictors of recurrence but also predictors of early recurrence. If we have reliable predictors of early recurrence, we can offer OLT to high-risk patients even before the actual recurrence appears.

In what case is hepatic resection a good option as a bridge therapy to transplantation?

In HCC patients enlisted for OLT, a significant problem is represented by the high drop-out from the waiting list due to progression of the tumour beyond Milan criteria. To solve this problem it has been suggested to use hepatic resection as a bridge for liver transplantation in those cases in which the expected waiting period will be longer than 6 months [25].

What is the role of systemic therapy for advanced HCC?

In recent years, several important intracellular signalling pathways such as the Ras/Raf/Mek/Erk and PI3k/Akt/mTOR pathway have been recognised, and the role of several growth factors and angiogenic factors such as ECF and vascular endothelial growth factor (VEGF) has been developed and widely tested in preclinical studies of HCC cell lines or xenograft models [38–41]. Several agents have entered clinical trials in HCC patients. Recently, a large, randomised, placebo-controlled trial has shown that a multikinase inhibitor targeting Ras-kinase and VEGFR-2, sorafenib, improves survival of patients with advanced HCC. Median overall survival was 10.7 months for sorafenib and 7.9 months for placebo ($p=0.0006$), which represents an increase of 44% [42]. Sorafenib was approved by regulatory agencies during 2007 and is likely to become the new standard therapy for HCC patients with advanced disease [43].

What is the role of adjuvant therapy after hepatic resection or ablation?

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HCC is characterised as a highly chemoresistant cancer with no effective systemic adjuvant therapy. Despite surgical or locoregional therapies, prognosis remains poor because of the high tumour recurrence or tumour progression. The oral administration of acyclic retinoids after hepatic resection is promising. This agent was associated with a significantly lower incidence of recurrence in a RCT compared with the placebo group (27% vs. 45%) [44]. TACE with lipiodol-iodine 131 significantly lowered recurrence rates and improved patient survival after liver resection for HCC [45, 46]. In an excellent Editorial titled “Interferon: the magic bullet to prevent HCC recurrence after resection?” [47], Clavien reviewed the 7 RCTs available on this topic. This author concluded that all 7 RCTs showed beneficial effects of adjuvant IFN treatment, either for the entire study population or defined subpopulations, after hepatic resection or ablation for HCC. The effect seems particularly striking for patients with pure HBV infections. These data are highly encouraging and should lead the search for new strategies, for example, by using a more stable formula and constant delivery of IFN through pegylated IFN, or through the use of nucleoside (e.g., lamivudine) or nucleotide (e.g., adefovir dipivoxil) analogues alone in HBV patients and the combination of IFN with ribavirin in HCV. Importantly, any new strategy must still be tested in RCTs, including a control group without treatment [47]. Another agent that has been tested in the adjuvant setting is PI-88, an antiangiogenic agent that inhibits VEGF and fibroblast growth factor types 1 and 2 (FGF-1 and FGF-2), and also blocks breakdown of the extracellular membrane by inhibiting heparinase. The latter mechanism stops the spread of tumour cells in addition to inhibiting angiogenesis. Previous studies with PI-88 have shown this agent to be well tolerated and to delay time to recurrence after surgery from 27 weeks to 48 weeks [48]. A global, randomised, phase 3 study is under way evaluating PI-88 vs. placebo in the adjuvant setting in patients with resected HCC. Although positive results have been reported for adjuvant therapies such as acyclic retinoids, interferon and other treatments in isolated RCTs, no adjuvant therapies are currently accepted as the standard of care for HCC patients who have undergone complete resection or local ablation.

Conclusions

In patients with HCC treated by hepatic resection, the survival prognostic factors are: HVPG >10 mmHg, the presence of margin invasion and satellites. The recurrence prognostic factors are: satellites, microvascular invasion, macrovascular invasion and absence of capsule. The identification of these survival and recurrence factors are crucial in order to identify those patients in whom salvage OLT must be considered even before the actual appearance of the recurrence. Measurement of HVPG improves survival but not recurrence rate. Our entire selection process fails to

improve recurrence. There is an urgent need to find effective adjuvant treatment after surgical resection of HCC in order to improve recurrence.

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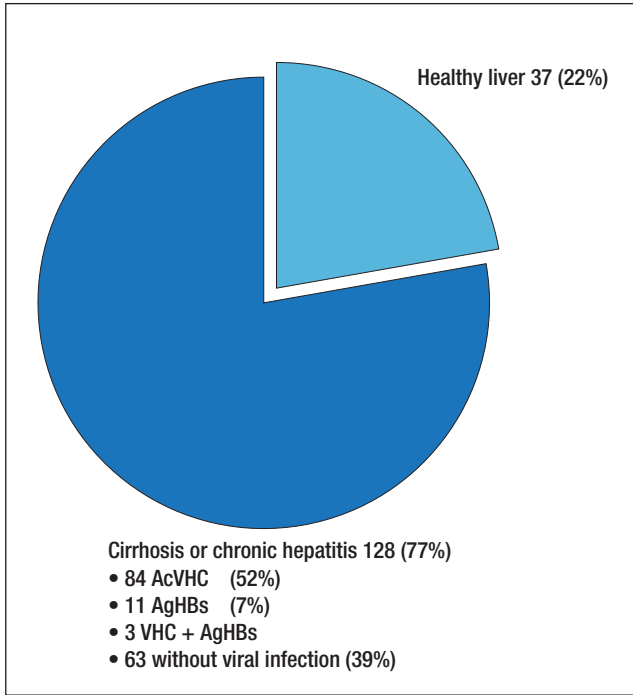


Fig. 1 Epidemiology of 165 HCCs operated on in the Bellvitge-Trueta Hospital from 1990 to 2007

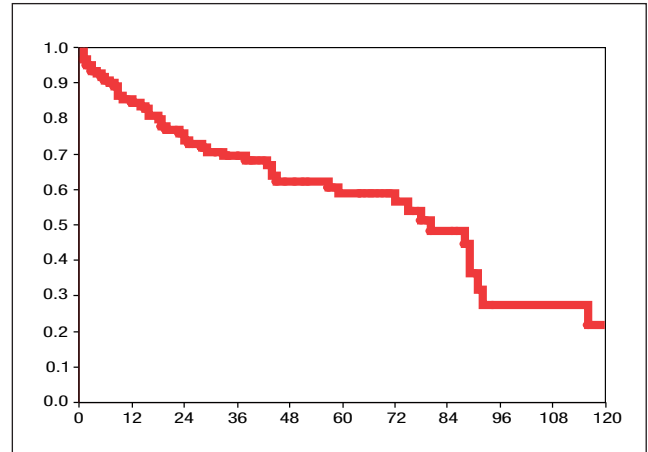


Fig. 3 Overall actuarial survival of 128 patients with CHC and cirrhosis

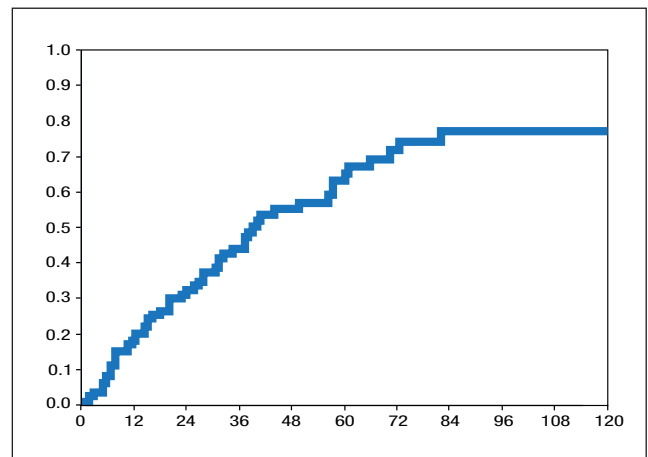


Fig. 4 Overall recurrence rate after resection in 128 patients with CHC and cirrhosis

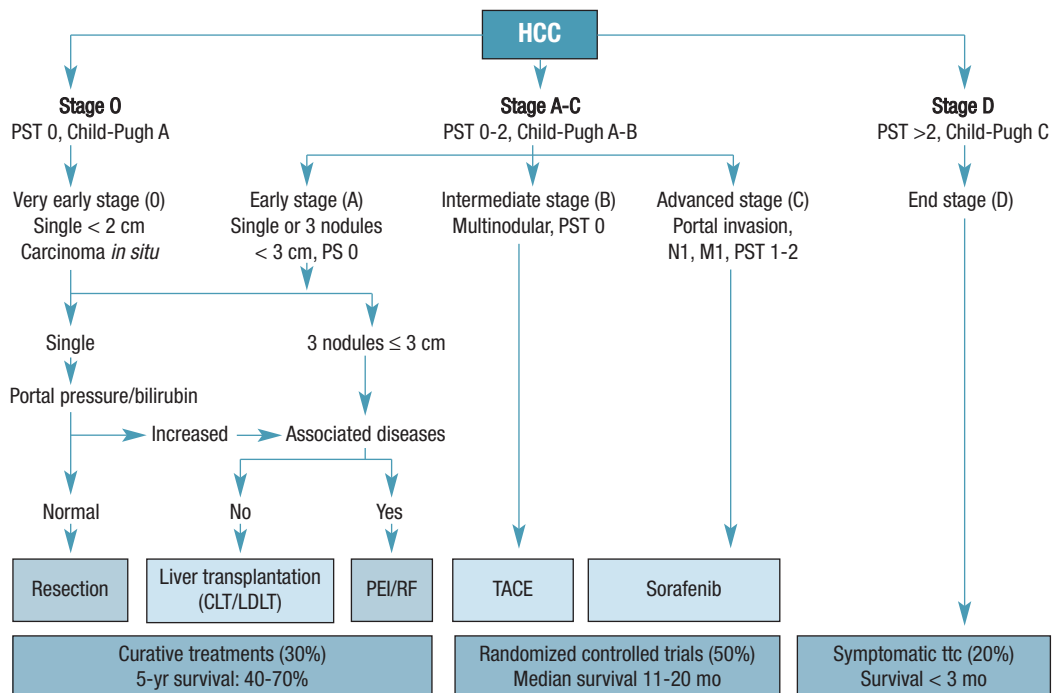


Fig. 2 Classification and algorithm of treatment of HCC according to BCLCG